composition to one including a vesicle-forming lipid derivatized with a polymer selected from polyglycolic acid (PGA), polylactic acid (PLA), a copolymer of PGA and PLA, polyvinyl alcohol and polyethylene glycol. Support for this amendment is found in claim 10, which has duly been canceled.

Claims 8 and 13 have additionally been amended to remove the term "severalfold" and to introduce the limitation that the composition is for able to accumulate in infected tissue after intraveneous administration. Basis for this amendment can be found, for example, at page 37, lines 23-26 and in Example 15 (pp. 86-87).

Accordingly, the amendments to the claims introduce no new matter.

II. Rejection Under 35 U.S.C. §112, first paragraph

Claims 8 and 11-19 were rejected under 35 U.S.C. §112, first paragraph as being non-enabled by the specification. More specifically, the Examiner asserts that the specification does not reasonable enable for the generic term " hydrophilic polymer" .

As discussed above, claims 8 and 13 have been amended to limit the hydrophilic polymer to those disclosed in the specification.

In view of the amendments to the claims, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

III. Rejection Under 35 U.S.C. §112, second paragraph

Claims 8-19 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner has objected to the term " severalfold" in the independent claim 8. The Examiner also objects to claim 1[3] for failure to recite a method of preparation step.

With respect to claim 8, the amendment to the claim, discussed above, removes the term " severalfold" .

With respect to claim 13, the applicants note that the claim recites the step of " entrapping the agent in liposomes" on line 5 (of the claim). Thus, the claim is directed to a method of preparing an agent for intraveneous injection, comprising entrapping the agent in the recited liposomes.

Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

IV. Double-Patenting Rejections

A. Rejection over U.S. Patent No. 5,103,556

Claims 8-12 and 14-17 were rejected under the judicially created doctrine of obviousness-type double patenting at being unpatentable over claims 1-33 of U.S. Patent No. 5,103,556 (hereinafter " the '556 patent").

The applicants respectfully traverse this rejection for the following reasons.

Claims 1-33 of the '556 patent describe a liposome composition composed of liposomes including a PEG-derivatized lipid and characterized by an improved blood circulation lifetime.

The claims of the present invention are directed to a liposome composition that is able to accumulate selectively at a site of infected tissue, to concentrate the liposome-entrapped drug at the infection site.

This feature is in no way suggested by the claims in the '556 patent.

Accordingly, the answer to the legal standard for determining if an obviousness-type double patenting rejection exists: " Does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent?" , is no. Because the '556 patent claims nowhere suggest that liposomes would accumulate in an infected tissue region to concentrate the administered drug, the present claims cannot be an obvious variation of the '556 claims.

For this reason, applicants' respectfully request reconsideration and withdrawal of the double-patenting rejection over the '556 patent.

B. Rejection over U.S. Patent No. 5,213,804

Claims 8-19 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting at being unpatentable over claims 1-15 of U.S. Patent No. 5,213,804 (hereinafter " the '804 patent").

The claims of the '804 patent are directed to a liposome composition for localizing a compound in a solid tumor. The liposomes include a polymer-derivatized lipid and are in a selected size of between 0.07-0.12 microns.

The claimed feature in the present invention that the liposomes are able to accumulate at a site of infected tissue is nowhere suggested by the claims in the '804 patent. Thus, it is the applicants' position that the pending claims cannot be considered to be an obvious variation of the claims of the '804 patent, since it is nowhere suggested in the '804 claims that liposomes could accumulate at an infected tissue region.

For this reason, applicants' respectfully request reconsideration and withdrawal of the double-patenting rejection over the '804 patent.

C. Rejection over application no. 09/139,158

Claims 8-19 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting at being unpatentable over claims 9-13 and 17-18 of co-pending application no. 09/139,158.

The applicants respectfully ask for clarification. Application serial number 09/139,158 is not, to the best of the applicants representative's knowledge, a co-pending application, or even an application handled by the firm of this representative. Applicants note that the serial number of the present application is 09/139,058. Clarification of this rejection is requested.

D. Rejection over U.S. Patent No. 5,843,473

Claims 8-19 were rejected under the judicially created doctrine of obviousness-type double patenting at being unpatentable over claims 1-33 of U.S. Patent No. 5,843,473 (application serial no. 07/858,171).

The present case is a divisional application of the 07/858,171 application, which matured into U.S. Patent No. 5,843,473. The presently pending claims were restricted in the parent case, as evidenced by the enclosed copy of the restriction requirement for the 07/858,171 application.

Accordingly, applicants request withdrawal of this double-patenting rejection over U.S. Patent No. 5,843,473.

V. Rejection under 35 U.S.C. §102

A. Rejection under 35 U.S.C. §102(b)

Claims 8-9 and 17 were rejected under 35 U.S.C. §102(b) as being anticipated by Sears (EP 0 118 316). This rejection is respectfully traversed for the following reasons.

1. The Claimed Invention

The invention as presently claimed in claim 8 is directed to a liposome composition for treating a systemic infection which is localized at a site other than the fixed macrophages residing in the liver or the spleen. The composition includes;

(i) liposomes composed of vesicle forming lipids, and including an amphipathic vesicle-forming lipid derivatized with polyglycolic acid, polylactic acid, a copolymer of polyglycolic acid and polylactic acid, polyvinyl alcohol or polyethylene glycol; the liposome having an extended blood circulation lifetime;

(ii) a therapeutic agent entrapped in the liposomes; and

(iii) an ability to accumulate in the infected tissue following intraveneous administration.

2. The Cited Sears Reference (EP 0118316)

Sears describes phospholipid compounds in which the polar-head group of a phospholipid is modified by covalent attachment of a polyalkylene glycol. The modified compounds, as described in Sears, are for use in forming micellar structures, as opposed to liposomal structures, when hydrated. Sears notes: " these structures are distinct and unique, as compared to liposomes or other lipid vehicles that are composed of phopshpatidylcholine" . (page 8, lines 31-33).

3. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 231 USPQ 81, 90 (Fed. Cir. 1986) *In re Donohue*, 766 F2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985). To anticipate a claim for a patent, a single prior source must contain all its essential elements.

The present invention as embodied in claims 8-19 includes at least three elements which are not taught in the Sears reference: (1) that the modified phospholipid is included in liposomal structures; (2) that the liposomes have a long blood circulation lifetime when compared to the liposomes in the absence of the derivatized lipid; and (3) that the liposomes are able to accumulate at a site of infected tissue.

As noted above, the Sears teaching is limited to micellar structures, and explicitly states that the structures formed using the modified lipids of his teaching " are distinct and unique as compared to liposomes" .

Further, there is no teaching in the Sears reference that the lipids would effect the blood circulation lifetime of either micellar or liposomal structures. Nor is there any teaching that such structures could effectively accumulate at a site of infection.

Because the standard of strict identity has not been met, the cited Sears reference cannot be said to anticipate claims 8-19.

B. Rejection under 35 U.S.C. §102(e)

Claims 8-9 and 11-19 were rejected under 35 U.S.C. §102(b) as being anticipated by Popescu *et al.* (U.S. Patent No. 4,981,692, hereinafter " Popescu"). This rejection is respectfully traversed for the following reasons.

1. The Present Invention

The presently claimed invention is discussed above.

2. The Popescu Reference

Popescu et al. ("Popescu") teaches the use of antibiotic-containing liposomes for treatment of infections, in particular, intracellular infections of the reticuloendothelial system, by intramammary infusion of liposomes.

The composition taught by Popescu is composed of liposomes formed from egg phosphatidylcholine (egg lecithin) and/or a variety of other phospholipids. The specification lists in column 4, lines 4-24, a large number of other lipid components that may optionally be included in the liposomes, including "polyethylene glycol derivatives of cholesterol (PEG-cholesterols), coprostanol, cholestanol or cholestane, and combinations of PC and cholesterol. They may also contain organic acid derivatives of sterols, such as cholesterol hemisuccinate (CHS), and the like."

3. Analysis

The standard for lack of novelty or anticipation is one of strict identity (*Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 231 USPQ 81, 90 (Fed. Cir. 1986), *In re Donohue*, 766 F2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985)). To anticipate a claim for a patent, a single prior art source must contain all its essential elements.

The following are elements/limitations of the claimed invention:

(i) liposomes containing a diacyl-chain amphipathic vesicle-

forming lipid derivatized with polyglycolic acid, polylactic acid, a copolymer of polyglycolic acid and polylactic acid, polyvinyl alcohol or polyethylene glycol;

(ii) the liposomes have an extended blood circulation lifetime;

(iii) the liposome after intraveneous administration accumulate in the infected tissue.

None of these elements are disclosed in Popescu. The teaching of Popescu is limited to PEG-cholesterol derivatives, and nowhere mentions a diacyl-chain lipid derivatized with PEG.

Examples 6 and 7 of the Popescu reference describe intravenous administration of the liposomes for treatment of Brucella. The treatment by intravenous administration of liposomes was ineffective to cure infection in both examples. As such, Popescu cannot be said to teach the use of intravenous administration of liposomes, for the treatment of infection.

Nor does Popescu teach the ability of liposomes having diacyl-chain-PEG components, when administered intravenously (or by any other method) to accumulate selectively in the infected tissue.

Since Popescu does not teach all of the elements of the claimed invention, it cannot anticipate the claimed invention under 35 U.S.C. §102(e).

Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(e).

VI. Rejection Under 35 U.S.C. §103

Claims 8-19 were rejected under 35 U.S.C. §103 as being obvious over Sears (EP 0 118 316).

Claims 8-19 were further rejected under 35 U.S.C. §103 as being obvious over Janoff (U.S. Patent No. 4,897,384) or Popescu (U.S. Patent No. 4,981,692) in view of Yoshioka (U.S. Patent No. 5,593,622).

These rejections are respectfully traversed for the following reasons.

A. The Present Invention

The present invention is discussed above.

B. The Cited Art

SEARS: The Sears reference is discussed above.

JANOFF describes a drug-ligand preparation where the preparation has less toxicity that than the drug alone (Col. 7, lines 19-23). The drugs for use in the invention of Janoff are those having an *in vivo* toxicity mediated through binding to lipid toxicity receptors (Col. 7, lines 25-30). A ligand, typically a lipid or lipid head group, capable of competitively binding to the toxicity receptor is co-administered with the drug to achieve the reduced toxicity (Col. 7, lines 35-44). The lipid then serves to prevent interaction between the drug and the receptor.

POPESCU: The Popescu reference is discussed above.

YOSHIOKA describes an agent for inhibiting adsorption of proteins on the surface of a liposomes. The agent consists of a compound having a hydrophobic moiety at one end and a hydrophilic macromolecular chain moiety at the other end. Preferred agents include PEG-derivatized phospholipids.

C. Analysis: Rejection Over Sears

As noted above, the teaching in the Sears reference is limited to micellar structures. There is no suggestion of using the modified phospholipids with stable, liposomal structures.

Moreover, the Sears reference is not concerned with increasing the blood circulation lifetime of liposomes, nor is there any suggestion in the reference that blood liposome levels could be increased by addition of the recited polymer moieties to the outer liposome surface.

More importantly, there is no suggestion in Sears that such liposomes would be able to accumulate at a site of infected tissue

to concentrate the liposome-entrapped drug at the infection.

For these reasons, pending claims 8-19 patentably define over the Sears reference.

C. Analysis: Rejection Over Janoff or Popescu in view of Yoshioka

It is the Examiner's position that the attachment of PEG to the surface of liposomes through coupling with the liposome phospholipid (as taught by Yoshioka), would have been an obvious modification to the liposomes of Janoff and Popescu, in view of Yoshioka's teaching that PEG prevents the adsorption of plasma proteins to the liposome surface and the subsequent agglutination.

The applicants disagree with this position for the following reasons.

First, as discussed above, the drug-ligand preparation described by Janoff is effective to reduce drug toxicity via competitive binding between the drug and the ligand (lipid or lipid head group) with the toxicity receptor. For example, Janoff describes a ligand for reducing toxicity of aminoglycoside drugs to be various phospholipids, and in particular phosphatidylinositol phosphate and phosphatidylinositol biphosphate, which are the putative toxicity receptors for aminoglycosides (Col. 9, lines 6-17).

Thus, an important feature of the Janoff preparation appears to be the ability of the selected ligand to competitively bind with the toxicity receptor. Modification of the phospholipid head group with a PEG chain, in accordance with the suggested modification in the Examiner's rejection, is nowhere suggested in Janoff; moreover such a modification of Janoff's preparation would likely alter its ability to competitively bind and reduce toxicity. In short, it is unclear if after such a modification of Janoff's preparation, functionality of the preparation to competitively bind would be retained.

Even if the Janoff preparation were modified to include PEG chains, the combined teachings of Janoff and Yoshioka still fail to

suggest (i) an increased blood circulation lifetime and (ii) accumulation of the liposomes at a site of tissue infection.

Similar reasoning applies to the combination of Popescu and Yoshioka. Popescu teaches a liposomal composition for use in treating infections which reside in the reticuloendothelial system (RES), specifically in macrophages (Col. 4, lines 49-64). As such, the composition described by Popescu is intended to be, after *in vivo* administration, taken up by phagocytic cells of the RES (Col. 5, lines 2-10). In contrast, the liposomes of the present invention are intended to avoid uptake by the RES, in order to concentrate the liposomes at a site of tissue infection. Modification of Popescu's formulation to include PEG-derivatized phospholipids, as suggested by the Examiner, would defeat its ability to be taken up by the RES, thereby defeating the intended purpose of the composition.

Furthermore, Popescu can be said to teach away from the applicants' invention as presently claimed, since Popescu demonstrates that intravenous administration of the liposomal formulation is not effective by itself to combat infection by Brucella (Examples 6 and 7), whereas the applicants show and claim intravenous administration of their liposomal formulation effective to combat infection, exemplified, for example, by infection by Klebsiella of the lung (Example 16 and Figure 19).

Nor is there any suggestion in Popescu or Yoshioka, taken alone or in combination, that liposomes having hydrophilic polymer chains would accumulate at a site of tissue infection.

Because the combination of references cited fails to teach and disclose the applicants' invention, it cannot be said that the invention is obvious. Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

IV. Conclusion

In view of the above remarks, the applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 324-0880.

Respectfully submitted,

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